Clinical Medicine

Long-Acting Nifedipine Versus Metoprolol as Monotherapy for Essential Hypertension

A Randomized, Controlled Crossover Study

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We assessed the efficacy of long-acting nifedipine as monotherapy in 52 patients with mild to moderate essential hypertension in a randomized, controlled crossover study. Good blood pressure control was achieved in 34 of 40 patients (85%) receiving nifedipine (mean daily dose, 52 mg in 2 divided doses) compared with 23 of 40 patients (58%) receiving metoprolol (mean daily dose, 155 mg in 2 divided doses). After treatment for 4 weeks, the mean blood pressures with nifedipine (149.7 ± 16.6/88.7 ± 11.1 mm of mercury) and metoprolol administration (163.9 ± 23.3/94.2 ± 10.2 mm of mercury) were significantly lower than with placebo (176.7 ± 17.3/100.9 ± 7.1 mm of mercury) (P < .05). The mean systolic pressure during nifedipine treatment was 14.2 mm of mercury lower (95% confidence interval [CI], 3.9 to 24.5 mm of mercury) and mean diastolic pressure 5.5 mm of mercury (95% CI, 0.3 to 10.7 mm of mercury) lower than with metoprolol therapy. Both drugs were reasonably well tolerated, and intolerance requiring withdrawal was encountered in 3 of 45 (7%) patients receiving nifedipine, compared with 1 of 45 (2%) of those taking metoprolol and placebo, respectively. Adverse effects of nifedipine, most of which were transient, included palpitations, headache, facial flushing, and ankle edema. Long-acting nifedipine is a promising agent when given alone for mild to moderate hypertension and can be safely administered in clinical practice.

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For the past two decades, diuretics and β-blockers have been commonly used as first-line drugs in treating hypertension.[1-3] Some large-scale long-term studies, however, have revealed certain side effects of the diuretics and β-blockers and shown that they are not well tolerated in certain patients.[4-7] These observations have stimulated interest in alternative drug regimens. Calcium antagonists have been found safe and effective in treating hypertensive crises and resistant hypertension, although experience using them as first-step monotherapy for hypertension is still limited.[8-10] With the availability of a slow-releasing and more convenient long-acting preparation of nifedipine, its use as a first-line drug for treating mild to moderate hypertension is theoretically appealing.[11,12]

In this article we report our experience with such a slow-releasing, long-acting preparation, nifedipine retard, as monotherapy for essential hypertension as compared with an established β-blocker, metoprolol.

Patients and Methods

After explaining the nature of the study and obtaining informed consent, we recruited 52 patients with mild to moderate essential hypertension seen in the hypertension clinic at the Prince of Wales Hospital (Hong Kong) between September 1985 and April 1987. Inclusion criteria were mild to moderate hypertension with a blood pressure of 160/95 to 219/114 mm of mercury for at least three readings on two separate occasions; age younger than 70 years; an absence of complications of hypertension, including myocardial infarction, renal impairment, heart failure, or cerebrovascular accident, and of other major systemic disease; and essential hypertension.

Patients with underlying causes, severe hypertension (blood pressure ≥220/115 mm of mercury), or contraindications for β-blockers were excluded from the study. Women included in the study were neither pregnant nor lactating.

During each visit, the blood pressure was measured at the same time of the day (10 AM to 12 noon) and at 12 hours after the last dose of pills. The same research nurse took all blood pressure measurements using a random-zero sphygmomanometer with the patient in the sitting position after five minutes of rest and after standing for two minutes. Korotkoff phase 5 was taken as the diastolic pressure, and the average of three readings was recorded in each posture.

After a run-in period of four weeks when no active treatment was given, patients were randomly divided into two

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TABLE 1.—*Blood Pressure (BP; mm of mercury) in Different Periods of Nifedipine, Metoprolol, and Placebo Treatment*

Patient Group and BP	First Phase: Placebo, Weeks 1-4	First Phase: Drug, Weeks 5-8	Second Phase: Placebo, Weeks 9-10	Second Phase: Drug, Weeks 11-14
Group A*				
Systolic	175.8±22.8	166.3±24.1†	177.4±32.7	149.8±19.1‡
Diastolic	101.8± 8.1	93.7± 7.8§	100.6±12.0	86.9±10.4‖
Group B¶				
Systolic	178.3±18.0	149.5±14.1†	170.9±23.7	161.6±22.8‡
Diastolic	101.6± 8.1	90.6±11.7§	98.5±10.3	94.7±12.3‖
P Value#	>.5		>.1	

*Metoprolol therapy, then nifedipine therapy.
†$P<.01$
‡$P<.05$
§$P>.1$
‖$P<.02$
¶Nifedipine therapy, then metoprolol therapy.
#Group A versus group B.

groups. Group A received titrated doses of 50 to 100 mg of metoprolol twice a day, and group B received 20 to 40 mg of nifedipine retard twice a day for four weeks to return the blood pressure to a normal range of 130/70 to 160/90 mm of mercury. A washout period of two weeks followed, after which patients were crossed over to the other drug, that is, nifedipine retard was administered to group A and metoprolol to group B for another four weeks. Patients were given a placebo tablet twice a day during the run-in and washout periods. So that their blood pressure response could be assessed during stress, patients were given a submaximal treadmill exercise test for eight to nine minutes using the Bruce protocol up to stage 3 on completion of the study while they were maintained on a regimen of one of the two drugs.

An electrocardiogram, chest x-ray film, and hematologic and biochemical profiles were carried out during each treatment period. At each visit an adverse effects questionnaire was administered, and any adverse symptoms were recorded in detail.

Six patients whose blood pressures returned to normal and one with a pressure of 220/115 mm of mercury or more during the second washout period were removed from the study. Five other patients requiring withdrawal because of adverse symptoms were excluded from the analysis of blood pressure responses, but they were included in the analysis of adverse side effects.

Paired t and χ^2 tests were used to assess the statistical significance of differences in blood pressure readings and adverse reactions.[13] Blood pressure results are given as the mean ± 1 standard deviation. The 95% confidence intervals (CI) for the difference in blood pressure readings were calculated.[14]

Results

Patients' ages ranged from 32 to 70 years with a mean of 54.3 ± 11.9 years. Of the 40 patients completing the two phases of study, 19 were men; 28 (70%) patients received 40 mg of long-acting nifedipine, 12 (30%) were given 80 mg of long-acting nifedipine, 18 (45%) received 100 mg of metoprolol, and 22 (55%) received 200 mg of metoprolol daily, all in two divided doses. Blood pressure levels are shown in Table 1. Good blood pressure control was achieved in 85% of patients receiving nifedipine, a mean daily dose of 52 mg in two divided doses, compared with 58% of patients taking metoprolol, a mean daily dose of 155 mg in two divided doses (Table 2). The mean sitting systolic blood pressure of patients taking nifedipine was 14.2 mm of mercury (95% CI, 3.9 to 24.5 mm of mercury) and the mean diastolic blood pressure was 5.5 mm of mercury (95% CI, 0.3 to 10.7 mm of mercury) lower than those of patients receiving metoprolol (Table 2, Figure 1). During treadmill exercise, the mean maximal blood pressure was similar with both drugs. No significant effect of the body posture on the blood pressure was seen with either drug, but the standing heart rates were slightly higher in the nifedipine and placebo periods than in the metoprolol period (Figure 2). Heart rates were lowest while patients received metoprolol ($P<.001$).

Of 45 patients, adverse symptoms were reported in 13 (29%) taking nifedipine compared with 7 (16%) receiving metoprolol ($P>.05$), 35% receiving placebo run-in, and 31% of patients on placebo washout ($P>.5$) (Table 3). These symptoms included facial flushing (4% nifedipine, 2% placebo) and ankle edema not associated with a significant increase in body weight (9% nifedipine). Headache was a common complaint, being present in 19% of patients receiving placebo, 4% of patients taking metoprolol, and 24% of those taking nifedipine. Some patients experienced dizziness (13% nifedipine, 11% to 15% placebo, 7% meto-

TABLE 2.—*Blood Pressure (BP; mm of mercury) Control With Nifedipine Therapy Versus Metoprolol Therapy**

Blood Pressure Indices	Patients: Metoprolol, Mean Dose 155 mg/d, No.	(%)	Nifedipine, Mean Dose 52 mg/d, No.	(%)
Excellent (≤140/80)	13	(32)	20	(50)
Good (140/80 to 155/90)	10	(25)	14	(35)
Overall	23	(58)	34	(85)
Mean systolic	163.9±23.3		149.7±16.6	
Difference (95% CI)	14.2 (3.9-24.5)†			
Mean diastolic	94.2±10.2		88.7±11.1	
Difference (95% CI)	5.5 (0.3-10.7)‡			
Baseline BP (at rest)§				
Mean maximum systolic	161.3±26.4		163.4±21.0	
Mean maximum diastolic	90.0±13.1		88.2± 7.2	
During exercise§				
Mean maximum systolic	189.3±17.9		192.5±18.8	
Mean maximum diastolic	93.7±13.4		94.2± 8.2	

CI=confidence interval
*Mean values are given as mean ± 1 SD.
†$P<.01$.
‡$P<.05$.
§$P>.1$ (nifedipine versus metoprolol).

prolol), tiredness (11% metoprolol, 4% nifedipine, 2% to 6% placebo), and palpitations (7% nifedipine, 2% to 4% placebo). Most symptoms were of minor inconvenience only. Withdrawal of drugs was required on five occasions, once each for palpitations, facial flushing, and headache during nifedipine therapy (three women); in one man because of headache during treatment with placebo; and in another man because of tiredness while receiving metoprolol. There were no notable changes in cardiac size, renal function, or other biochemical indices, including cholesterol and random glucose levels, during treatment with either drug (Table 4).

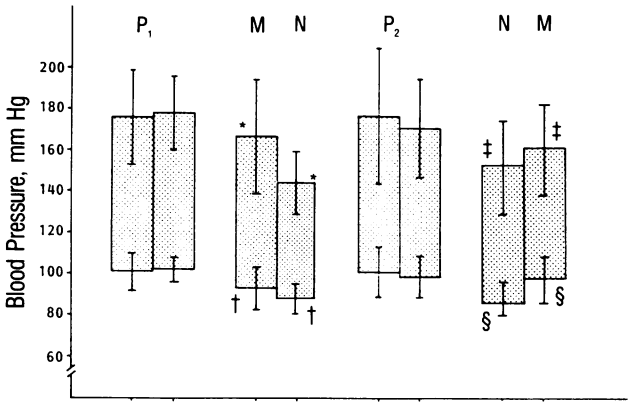

Figure 1.—The graphs show blood pressures during placebo run-in (P_1), placebo washout (P_2), metoprolol (M), and nifedipine (N) periods. * = $P<.01$, † = $P>.1$, ‡ = $P<.05$, § = $P<.02$

TABLE 3.—*Patients Having Side Effects in Different Periods of Nifedipine, Metoprolol, and Placebo Treatment*

	Placebo		Metoprolol	Nifedipine
	Run-in	Washout		
Side Effect	*No. (%)*	*No. (%)*	*No. (%)*	*No. (%)*
Gastrointestinal upset	3 (6)	0 (0)	4 (9)	3 (7)
Flushing	1 (2)	0 (0)	0 (0)	2 (4)*
Edema	0 (0)	0 (0)	0 (0)	4 (9)
Headache	10 (19)	8 (18)*	2 (4)	11 (24)*
Dizziness	8 (15)	3 (7)	3 (7)	6 (13)
Tiredness	3 (6)	1 (2)	5 (11)*	2 (4)
Palpitations	2 (4)	1 (2)	1 (2)	3 (7)*
Other	11 (21)	5 (11)	8 (18)	14 (31)
Withdrawal from study	0 (0)	1 (2)	1 (2)	3 (7)
None	34 (65)	31 (69)	38 (84)	32 (71)
Total count	52	45	45	45

*One patient withdrew because of adverse effects.

Discussion

In our study we were able to objectively evaluate the efficacy and safety of a new long-acting, slow-releasing preparation of nifedipine in patients with mild to moderate essential hypertension. Blood pressure was measured objectively with a random zero sphygmomanometer; thus, any digit preference or observer bias of either tested drug was minimized. To ensure a fair comparison of the potencies of these two drugs, only 40 patients who completed both phases of therapy were included, and 7 patients whose blood pressures remained normal or too high during the second placebo washout period were excluded. Of the latter patients, three had metoprolol and four had nifedipine as their first active drug, and their exclusion probably did not distort or affect the overall evaluation.

This study shows that the long-acting preparation of nifedipine is an effective antihypertensive drug and perhaps more potent than the commonly used β-blocker, metoprolol.[15,16] When nifedipine was used as monotherapy, blood pressures returned to normal in 85% of patients with mild to moderate essential hypertension compared with 58% of patients taking metoprolol alone. This range of potency compares favorably with that of many other antihypertensive agents and is similar to that reported with the use of alternative calcium channel blockers such as verapamil and diltiazem.[10,17,18] The response rate to metoprolol therapy (58%) is similar to that reported from many studies in western countries.[15,16]

Adverse effects were often transient, and most were rea-

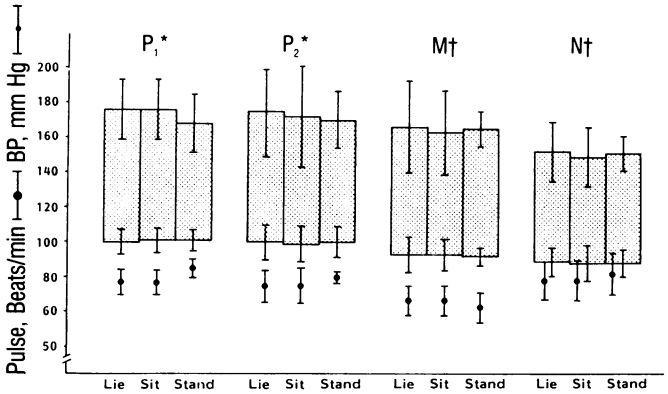

Figure 2.—The graphs show blood pressures and pulse rates in different postures. The *P* values in different periods refer to comparisons between the corresponding systolic and diastolic blood pressures in different postures. * = $P>.05$, † = $P>.1$

TABLE 4.—*Biochemical and Radiologic Profiles of Patients Receiving Placebo, Metoprolol, and Nifedipine (Mean ± 1 SD)**

	Placebo			
Laboratory and X-Ray Variable	*Run-in*	*Washout*	*Metoprolol*	*Nifedipine*
Potassium, mmol/liter	3.9 ± 0.4	4.0 ± 0.5	4.1 ± 0.5	3.7 ± 0.3
Calcium, mmol/liter	2.4 ± 0.1	2.4 ± 0.9	2.3 ± 0.1	2.3 ± 0.1
Urea nitrogen, mmol/liter	5.9 ± 1.4	6.3 ± 1.5	6.3 ± 1.5	6.3 ± 1.5
Creatinine, μmol/liter	81.0 ±21.7	81.7 ±13.5	81.7 ±16.7	78.6 ±20.4
Urate, mmol/liter	0.37± 0.09	0.39± 0.08	0.39± 0.08	0.37± 0.07
Glucose, mmol/liter	5.2 ± 1.3	5.2 ± 1.0	5.1 ± 1.1	5.1 ± 1.0
Cholesterol, mmol/liter	5.9 ± 1.0	5.5 ± 1.3	5.1 ± 1.3	5.5 ± 1.1
Chest x-ray†	51.0 ± 3.9	51.8 ± 1.6	52.5 ± 3.7	49.2 ± 3.4

*Metoprolol or nifedipine versus placebo, $P>.1$.
†The numbers represent the cardiothoracic ratio.

sonably well tolerated. The side-effect profile of this slow-releasing preparation appears to be better than that reported with plain nifedipine preparations.[19] A number of untoward reactions, as revealed by answers to the questionnaire, were also present during the two placebo periods, illustrating the justification and importance of including such control periods in any critical evaluation. Some of these adverse effects, such as headache and dizziness, could be related to high blood pressure. Specific adverse reactions to nifedipine included facial flushing and headache, which have also been reported with the use of other calcium channel blockers and presumably are related to excessive vasodilation in sensitive subjects.[10,20] The exact mechanism of ankle edema is still not well defined. It was not associated with an increase in body weight and is therefore unlikely to be related to pseudotolerance with fluid retention. Its presence usually requires nothing more than reassuring patients of its benign nature. Although we saw no significant changes in heart rates with the use of nifedipine as compared with placebo, three patients (7%) experienced palpitations, presumably due to reflex tachycardia, and withdrawal of one patient was required. Previous studies have reported either no change or a mild increase in heart rates, the differences perhaps being explained by patient selection or study design.[21,22] Freedom from cardiac slowing with the use of nifedipine may have appeal in the setting of bradyarrhythmias, conduction disorders, or when combination therapy with β-blockers is being contemplated. No postural change in blood pressure or any adverse biochemical changes were encountered, and tachyphylaxis was not seen. Gastrointestinal upset such as constipation and cardiac-slowing effect have been reported with the use of verapamil and diltiazem, but, on the whole, their acceptance rates are similar.[17,20]

A twice-a-day regimen of long-acting nifedipine is more convenient than the plain capsule taken three or four times a day, and patients' compliance is likely to be greater with this regimen. Nifedipine is relatively more expensive, however, than other common step-one medications, which could limit its wider use as initial monotherapy in many developing countries with limited financial resources. A greater therapeutic prospect for calcium antagonists as step-one therapy may be the presence of coexisting diseases including ischemic heart disease, chronic obstructive airway disease, or peripheral vascular disease, where beneficial actions on vascular or bronchial smooth muscles are particularly appealing.[23-25] Some preliminary reports have suggested a vascular protective effect by nifedipine in vitro and in animal models, which, if confirmed in humans, could be an additional bonus of this group of drugs in the treatment of hypertension.[26] The implications of such therapy in the primary prevention of coronary artery disease and general atherosclerosis in hypertensive patients is certainly exciting but remains to be proved.

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